PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P26915PC01/RKI	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/NL2005/000026	International filing date *(day/month/year)* 14.01.2005	Priority date *(day/month/year)* 16.01.2004
International Patent Classification (IPC) or national classification and IPC C12N5/08, C12N5/06, A61P17/02		
Applicant VERENIGING VOOR CHRISTELIJK ... et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in Item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.11.2005	16.02.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Teyssier, B Telephone No. +31 70 340-2062

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NL2005/000026

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-27 as originally filed

Claims, Numbers

1-21 received on 18 11.2005 with letter of 18.11.2005

Drawings, Sheets

1 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 17-21

because:

☒ the said international application, or the said claims Nos. 17-21 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/NL2005/000026

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 17-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1 Basset-Séguin N et al., *Differentiation* September 1990, 44(3), 232-238
D2 Lee D-Y et al., *Journal of Dermatological Science* June 2000, 23(2), 132-137
D3 Chakrabarty K H et al., *Journal of Dermatology* November 1999, 141(5), 811-823
D3a Ghosh M M et al., *Annals of Plastic Surgery* October 1997, 39(4), 390-4
D4 Ralston D R et al., *Journal of Dermatology* April 1999, 140(4), 605-615
D5 Krejci N C et al., *Journal of Investigative Dermatology* November 1991, 97(5), 843-848
D6 Ponec M et al., *Skin Pharmacology & Applied Skin Physiology* Dec. 2002, 15(Suppl. 1), 4-17

D5 (p. 844) teaches the preparation of skin equivalents by cultivating fibroblasts and keratinocytes onto DED; keratinocytes, when used, are seeded in the same place, and thus on the same side, of the DED. D1 teaches a simplified method for preparing artificial skin for transplantation by growing skin punches biopsies, which comprises both a dermal and an epidermal layer, from the subject, onto de-epidermised donor dermis (DED). While the methods of D1 and D5 differ from the method of present claims 1-15 in that fibroblasts and keratinocytes contact the same side of the DED connective layer, it may be observed that, according to D3a (p. 398, fig. 3A), when fibroblasts and keratinocytes are cultured simultaneously on the papillary surface of DED fibroblasts do cross the basement membrane and grow within the DED so that the resulting reconstituted skin of D1 and D5 will consist of a DED layer populated by fibroblasts and an epidermal layer on top of the basement membrane attached to the DED and will thus be structurally similar to the product of claim 16.

D2 teaches the preparation of a skin equivalent by contacting a sheet of DED with fibroblasts in a collagen matrix on one side and keratinocytes on the other side. D3 (p. 814, referring back to D3a as ref. 10, for further details), D3a (p. 394, protocol 4) and D4 (p. 606) teach the preparation of skin equivalents by cultivating fibroblasts onto the reticular surface of DED for two days before cultivating

keratinocytes onto the papillary surface.

The subject-matter of independent claim 1 differs from D2-D4 in that an intact epithelial layer is used instead of isolated keratinocytes and is thus novel (Article 33(2) PCT). The skilled person wanting to simplify the method of D2 would find in D1 some incentive for using pieces of whole tissues rather than cultivated cells, but D1 teaches the use of whole biopsies, comprising both an epidermal and a dermal layer, rather than of an epidermal layer dissociated from the dermal layer, as in the process of the invention. Thus the process of the invention is not derivable from any of the prior art documents (D3 or D4 possibly being closest) even in combination with D1 and an inventive step can be acknowledged for the subject-matter of claims 1-15 (Article 33(3) PCT).

It has been submitted that the "product-by-process" of claim 16 can be distinguished from the prior art skin equivalents of D1-D5 because biopsies edges remain visible. While this appears to relate to mere artifacts from the manufacturing process rather than to substantive structural differences, which would endow the product of the invention with different, or improved, therapeutic abilities over the prior art, novelty and inventivity of claim 16 may be acknowledged under the PCT Guidelines. National law of PCT Contracting States may provide for different criteria.

D6 was cited solely to illustrate that the particular culture medium used in the examples is not novel.

For the assessment of the present claims 17-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims.